THE RISK OF STOMACH CANCER IN PATIENTS WITH GASTRIC OR DUODENAL ULCER DISEASE

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ABSTRACT

Background *Helicobacter pylori* infection, now considered to be a cause of gastric cancer, is also strongly associated with gastric and duodenal ulcer disease. The discovery of these relations has brought the long-controversial connection between peptic ulcers and gastric cancer into focus.

Methods We estimated the risk of stomach cancer in a large cohort of hospitalized patients with gastric or duodenal ulcers, as recorded in the Swedish Inpatient Register between 1965 and 1983. Altogether, 57,936 patients were followed through 1989, for an average of 9.1 years. The standardized incidence ratio — the ratio of the observed number of cancers to the number expected on the basis of the incidence in the Swedish population at large — was used as a measure of relative risk.

Results After peaking in the first 3 years of follow-up, the standardized incidence ratio for gastric cancer among 29,287 patients with gastric ulcers leveled off at 1.8 (95 percent confidence interval, 1.6 to 2.0) and remained significantly increased throughout follow-up, which was as long as 24 years for some patients. Prepyloric ulcer, diagnosed in 8646 patients, was not associated with a significant excess risk (standardized incidence ratio, 1.2; 95 percent confidence interval, 0.8 to 1.6). In the cohort of patients with duodenal ulcers (24,456 patients), the incidence of gastric cancer was significantly lower than expected. After the second year of follow-up, the standardized incidence ratio was only 0.6 (95 percent confidence interval, 0.4 to 0.7) and remained stable thereafter.

Conclusions Gastric ulcer disease and gastric cancer have etiologic factors in common. A likely cause of both is atrophic gastritis induced by *H. pylori*. By contrast, there appear to be factors associated with duodenal ulcer disease that protect against gastric cancer. (N Engl J Med 1996;335:242-9.)

THE relation between peptic ulcer and gastric carcinoma has long been a matter of controversy.[1] A coexisting gastric cancer has been reported in 2 percent of patients given a diagnosis of gastric ulcers,[2] but follow-up studies have failed to demonstrate any increased long-term risk of gastric cancer in patients with gastric ulcers.[3-8]

By contrast, duodenal ulcer disease has often been inversely associated with gastric cancer, but the evidence comes largely from small studies or case series.[9,10] *Helicobacter pylori* infection is now recognized as an important causative factor in both duodenal ulcers[11] and gastric cancer,[12] contrary to what might be inferred from a negative association between duodenal ulcers and gastric cancer. Determining the risk of gastric cancer in patients with duodenal or gastric ulcers may shed light on this puzzle and on important aspects of gastric carcinogenesis. We therefore investigated the risk of gastric cancer during long-term follow-up of a large, population-based cohort comprising patients hospitalized for gastric or duodenal ulcers who had not received surgical treatment.

METHODS

The Study Population

Since 1964, the Swedish National Board of Health and Welfare has compiled data on individual hospital discharges in its Inpatient Register.[13] Besides a national registration number (uniquely identifying every resident of Sweden), each record contains medical data, including surgical procedures performed (coded according to the Swedish Classification of Operations and Major Procedures) and diagnoses at discharge (coded through 1968 according to the *International Classification of Diseases, 7th Revision* [ICD-7][14] and according to the *8th Revision* [ICD-8][15] thereafter). In 1983 the register covered 85 percent of the Swedish population. Since there is virtually no private hospital care in Sweden and since all patients are obliged to use a hospital within the county where they reside, any study using the Inpatient Register is, in effect, population-based.

The Cohort

All patients in the Inpatient Register who survived to be discharged between 1965 and 1983 with a diagnosis of peptic ulcers (ICD-7 code 540 or 541, ICD-8 code 531 or 532) were considered for inclusion in the cohort. From 1968 on, special ICD-8 codes — 531.00, 531.90, 531.91, and 531.92 — were used for prepyloric gastric ulcers. For each potential subject, we identified the index episode — the first recorded hospitalization for peptic ulcer. Patients who underwent gastric resection or vagotomy before their first discharge (16,989 patients) were not eligible, nor were the 298 patients in whom gastric cancer was diagnosed before or at the time of the index episode.

We assessed 59,341 records with unique national registration

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numbers that might identify potentially eligible subjects. For each of these records the national registration number was checked in other registers — for instance, the Register of the Total Population. National registration numbers that could not be located in any of the other registers were deemed invalid and excluded. A total of 1405 records (2.4 percent) were excluded for this and other related reasons.

The final cohort comprised 29,287 patients (17,073 men and 12,214 women) with gastric ulcers, 24,456 patients (17,221 men and 7235 women) with duodenal ulcers, and 4193 patients (2915 men and 1278 women) with both gastric and duodenal ulcers. This last group was analyzed separately. Data from patients with both types of ulcers were not included in the analysis of either patients with gastric ulcers or patients with duodenal ulcers. The index episode of hospitalization was for bleeding in 25,997 patients (45 percent) and for perforation in 4515 (8 percent). Other characteristics of the patients in the cohort are given in Table 1. The basis for the diagnosis given a patient was not recorded in the Register, but during the first part of the study period (1965 through 1975) there was a record of at least one in-hospital gastroscopy for 23 percent of the patients with a diagnosis of gastric ulcers and for 17 percent of those with duodenal ulcers. During the second part of the study (1976 through 1983), the corresponding figures were 41 percent for patients with gastric ulcers and 38 percent for those with duodenal ulcers.

Follow-up

The national registration numbers, linked to the nationwide registries of migration and cause of death, gave us information on dates of emigration and death. The national Swedish Cancer Registry, founded in 1958 and including more than 98 percent of all cases of cancer in the country,[16] was examined to identify all cases of gastric cancer in the cohort. Since 1970, the Cancer Registry has used a special code to indicate tumors located in the gastric cardia. The patients in the cohort were followed up from the date of their first hospital admission for peptic ulcer until the date of emigration, death, a gastric resection or vagotomy before December 31, 1983, or a diagnosis of gastric cancer, or until December 31, 1989, whichever occurred first. Because only the Inpatient Register — and not the registries used for follow-up — had data on surgical procedures in the cohort, information on operations performed after 1983 was not available to us.

Among the 24,681 patients who were assigned to the cohort because of an index hospitalization between 1965 and 1975, follow-up ended with a gastric resection or vagotomy before the end of 1983 in 13 percent of the patients with gastric ulcers (1629, of whom 877 were operated on within six months of the index episode) and in 19 percent of the patients with duodenal ulcers (2051, of whom 952 were operated on within six months). Among the 33,255 members of the cohort whose index hospitalization occurred from 1976 through 1983, follow-up was terminated because of a resection or vagotomy before the end of 1983 in 9 percent of the patients with gastric ulcers (1599, of whom 867 were operated on within six months) and in 12 percent of the patients with duodenal ulcers (1696, of whom 885 were operated on within six months).

Statistical Analysis

Malignant gastric ulcers are sometimes misdiagnosed as benign ulcers. It is not known how long it takes to identify correctly all

TABLE 1. CHARACTERISTICS OF THE STUDY COHORT.

CHARACTERISTIC	GASTRIC ULCERS			DUODENAL ULCERS (N=24,456)	GASTRIC AND DUODENAL ULCERS (N=4193)
	PREPYLORIC (N=8646)	OTHER (N=20,641)	TOTAL (N=29,287)		
Sex — no.					
Male	5,449	11,624	17,073	17,221	2,915
Female	3,197	9,017	12,214	7,235	1,278
Person-years of follow-up	74,858	169,026	243,884	246,177	39,351
Average date of index hospitalization	5/77	11/76	1/77	7/76	5/76
Average length of follow-up — yr	8.7	8.2	8.3	10.1	9.4
Age at index hospitalization — no. (%)					
<40 Yr	693 (8.0)	1,274 (6.2)	1,967 (6.7)	3,751 (15.3)	426 (10.2)
40–49 Yr	908 (10.5)	1,824 (8.8)	2,732 (9.3)	3,266 (13.4)	478 (11.4)
50–59 Yr	1,704 (19.7)	3,600 (17.4)	5,304 (18.1)	4,913 (20.1)	795 (19.0)
60–69 Yr	2,298 (26.6)	5,268 (25.5)	7,566 (25.8)	5,621 (23.0)	1,053 (25.1)
70–79 Yr	2,103 (24.3)	5,857 (28.4)	7,960 (27.2)	5,004 (20.5)	1,017 (24.3)
≥80 Yr	940 (10.9)	2,818 (13.7)	3,758 (12.8)	1,901 (7.8)	424 (10.1)
Average age at index hospitalization — yr	62.4	64.6	63.9	58.2	61.4
Average age at diagnosis of stomach cancer — yr	68.4	70.3	70.0	71.6	68.2
Reason for index hospitalization — no. (%)					
Bleeding	4,160 (48.1)	8,394 (40.7)	12,554 (42.9)	11,659 (47.7)	1,784 (42.5)
Perforation	1,045 (12.1)	1,445 (7.0)	2,490 (8.5)	1,785 (7.3)	240 (5.7)
Stenosis	578 (6.7)	0	578 (2.0)	1,118 (4.6)	275 (6.6)
Other	2,863 (33.1)	10,802 (52.3)	13,665 (46.7)	9,894 (40.5)	1,894 (45.2)
Gastric resection 1965–1983 — no. (%)*	1,148 (13.3)	2,282 (11.1)	3,430 (11.7)	3,114 (12.7)	1,186 (28.3)
Vagotomy 1965–1983 — no. (%)*	143 (1.7)	136 (0.7)	279 (1.0)	946 (3.9)	216 (5.2)

*Data were censored from the date of operation.

the overlooked cancers in a given group of patients. We therefore computed estimates of risk for the subjects with gastric ulcers for each of the first five years of follow-up and found that the initially high values declined with time and leveled off after three years of follow-up. Duodenal ulceration is less likely to be confused with gastric cancer; nevertheless, the estimates of risk for patients with duodenal ulcers also dropped substantially during the first two years of follow-up and then remained stable. Since a transient peak in the incidence of a disease soon after the initial hospitalization is likely to reflect a selection bias rather than underlying risk factors, we performed separate analyses of follow-up before and after the point at which the level of risk stabilized.

The expected number of cancers was calculated on the basis of the incidence of cancer in the Swedish population at large, adjusted for sex and age (in five-year groups) for each calendar year of observation. The standardized incidence ratio — the ratio of the observed to the expected number of cancers — was used as a measure of relative risk. The 95 percent confidence intervals for the standardized incidence ratios were calculated on the assumption that the observations conformed to a Poisson distribution.[17]

To separate out the effects of the explanatory variables, a multivariate model was created with an assumption of a multiplicative effect on the standardized incidence ratio for each variable. The number of observed cases was assumed to conform to a Poisson distribution, and the model was assessed with maximum-likelihood methods and generalized linear analysis. Grouped data were categorized as in Table 5. The deviance was used in testing the effects of individual variables in addition to direct inference based on parameter estimates and standard errors. The degree of absolute fit of the model was measured with the Pearson chi-square statistic. Because the pattern of risk was different during the first few years of follow-up, the model was based on follow-up of two years or more.

RESULTS

Patients with Gastric Ulcers

Among 29,287 patients with gastric ulcers only, followed for an average of 8.3 years, gastric cancer developed in 782 (standardized incidence ratio, 4.3; 95 percent confidence interval, 4.0 to 4.6). Figure 1 shows the standardized incidence ratios according to length of follow-up. During the first three years of follow-up, gastric cancer was diagnosed in 561 (1.9 percent) of the members of the cohort with gastric ulcers, corresponding to a risk almost 10 times that of the Swedish population at large, as adjusted for age and sex. A total of 221 gastric cancers developed after more than three years of follow-up, as compared to 124 expected cancers, to yield a standardized incidence ratio of 1.8 (95 percent confidence interval, 1.6 to 2.0) (Table 2). Between years 3 and 24 of follow-up, the relative risk was higher among women than among men ($P = 0.02$).

The standardized incidence ratio among 8646 patients with prepyloric ulcers was 1.2 (95 percent confidence interval, 0.8 to 1.6) after the third year of follow-up (Table 2). In this subgroup as well, the relative risk was higher among women than among men ($P = 0.021$). Thus, the increased long-term risk of gastric cancer among patients with gastric ulcers seemed to be confined to those with an ulcer that was not located in the prepyloric region (standardized incidence ratio, 2.0; 95 percent confidence interval, 1.8 to 2.4).

In analyses stratified according to the reason for the index hospitalization (bleeding, perforation, or ulcer without complication) and the year of diagnosis (1965 through 1975 or 1976 through 1983), the standardized incidence ratios in the subgroups were similar to those in the entire cohort of patients with gastric ulcers (data not shown). The standardized incidence ratios were consistently higher in patients who were younger at the start of follow-up (Table 3).

After the third year of follow-up, cancer of the gastric cardia developed in 19 patients with gastric ulcers, although only 11 would be expected (standardized incidence ratio, 1.8; 95 percent confidence interval, 1.1 to 2.8). In subsequent consecutive follow-up periods, the standardized incidence ratio tended to decline (data not shown).

Patients with Duodenal Ulcers

Of the 24,456 patients with duodenal ulcers only, followed for an average of 10.1 years, gastric cancer developed in 136 (standardized incidence ratio, 0.9; 95 percent confidence interval, 0.7 to 1.1). A higher number of tumors was noted shortly after the index hospitalization, but the standardized incidence ratio leveled off after two years (Fig. 1). The relative risk 2 to 24 years after the index hospitalization was significantly decreased in men (standardized incidence ratio, 0.5; 95 percent confidence interval, 0.4 to 0.7) (Table 4). In women, however, the decrease in risk did not quite reach statistical significance (standardized incidence ratio, 0.7; 95 percent confidence interval, 0.4 to 1.1).

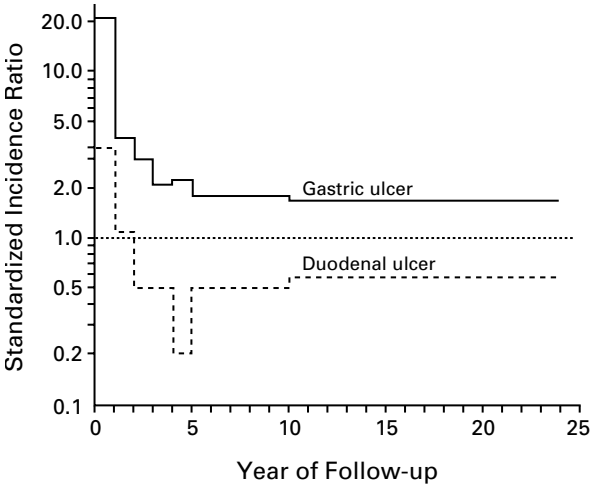

Figure 1. Standardized Incidence Ratio for Gastric Cancer in Patients with Gastric or Duodenal Ulcers, According to the Year of Follow-up.

The scale for the standardized incidence ratio is logarithmic.

TABLE 2. STANDARDIZED INCIDENCE RATIO (SIR) FOR GASTRIC CANCER AMONG PATIENTS WITH GASTRIC ULCERS, ACCORDING TO SEX AND YEAR OF FOLLOW-UP.*

GROUP	MEN		WOMEN		TOTAL	
	NO. OF CASES	SIR (95% CI)	NO. OF CASES	SIR (95% CI)	NO. OF CASES	SIR (95% CI)
All gastric ulcers†						
Years of follow-up						
0–2	354	8.9 (8.0–9.9)	207	11.1 (9.6–12.7)	561	9.6 (8.8–10.4)
3–4	35	1.6 (1.1–2.2)	33	3.2 (2.2–4.4)	68	2.1 (1.6–2.7)
5–9	64	1.7 (1.3–2.1)	33	1.9 (1.3–2.6)	97	1.7 (1.4–2.1)
10–24	37	1.5 (1.0–2.0)	19	1.8 (1.1–2.9)	56	1.6 (1.2–2.0)
3–24	136	1.6 (1.3–1.9)	85	2.2 (1.8–2.7)	221	1.8 (1.6–2.0)
Prepyloric ulcers‡						
Years of follow-up						
0–2	62	5.1 (3.9–6.6)	35	7.5 (5.2–10.4)	97	5.8 (4.7–7.1)
3–4	7	1.0 (0.4–2.1)	4	1.5 (0.4–3.8)	11	1.1 (0.6–2.0)
5–9	14	1.1 (0.6–1.9)	11	2.4 (1.2–4.3)	25	1.5 (0.9–2.2)
10–24	4	0.5 (0.1–1.3)	3	1.2 (0.2–3.5)	7	0.7 (0.3–1.4)
3–24	25	0.9 (0.6–1.4)	18	1.9 (1.1–2.9)	43	1.2 (0.8–1.6)
Other gastric ulcers§						
Years of follow-up						
0–2	292	10.6 (9.4–11.9)	172	12.3 (10.5–14.2)	464	11.2 (10.2–12.2)
3–4	28	1.9 (1.2–2.7)	29	3.7 (2.5–5.3)	57	2.5 (1.9–3.2)
5–9	50	1.9 (1.4–2.5)	22	1.7 (1.1–2.5)	72	1.8 (1.4–2.3)
10–24	33	1.9 (1.3–2.7)	16	2.0 (1.2–3.3)	49	1.9 (1.4–2.6)
3–24	111	1.9 (1.6–2.3)	67	2.3 (1.8–3.0)	178	2.0 (1.8–2.4)

*CI denotes confidence interval.

†The group included 29,287 patients (17,073 men and 12,214 women).

‡The group included 8646 patients (5449 men and 3197 women).

§The group included 20,641 patients (11,624 men and 9017 women).

Stratification according to the reason for the index hospitalization and the year of diagnosis did not reveal any important differences in the relative risk of cancer (data not shown). The risk was also not comparatively reduced in the youngest group of patients with duodenal ulcers (those less than 50 years old at the time of the index hospitalization), but this estimate is unreliable because of the small number of observations (data not shown). In the cohort with duodenal ulcers, cancer of the gastric cardia developed in 9 patients after the second year of follow-up, as compared with an expected 11 patients (standardized incidence ratio, 0.8; 95 percent confidence interval, 0.4 to 1.5).

Patients with Both Types of Ulcer

Among the 4193 patients who were hospitalized for a combination of gastric and duodenal ulcers,

TABLE 3. STANDARDIZED INCIDENCE RATIO (SIR) FOR GASTRIC CANCER AMONG PATIENTS WITH GASTRIC ULCERS, ACCORDING TO AGE AT INDEX HOSPITALIZATION AND YEAR OF FOLLOW-UP.*

YEAR OF FOLLOW-UP	AGE					
	<50 YR (N=4699)		50–69 YR (N=12,870)		>69 YR (N=11,718)	
	NO. OF CASES	SIR (95% CI)	NO. OF CASES	SIR (95% CI)	NO. OF CASES	SIR (95% CI)
0–2	52	72.5 (54.1–95.1)	215	13.1 (11.4–14.9)	294	7.1 (6.4–8.0)
3–4	3	5.1 (1.0–14.9)	25	2.2 (1.4–3.2)	40	2.0 (1.4–2.7)
5–9	7	4.1 (1.7–8.5)	54	2.0 (1.5–2.7)	36	1.3 (0.9–1.8)
10–24	5	1.6 (0.5–3.6)	40	1.6 (1.2–2.2)	11	1.3 (0.7–2.4)
3–24	15	2.7 (1.5–4.5)	119	1.9 (1.6–2.3)	87	1.5 (1.2–1.9)

*CI denotes confidence interval.

TABLE 4. STANDARDIZED INCIDENCE RATIO (SIR) FOR GASTRIC CANCER AMONG PATIENTS WITH DUODENAL ULCERS, ACCORDING TO SEX AND YEAR OF FOLLOW-UP.*

YEAR OF FOLLOW-UP	MEN (N=17,221)		WOMEN (N=7235)		TOTAL (N=24,456)	
	NO. OF CASES	SIR (95% CI)	NO. OF CASES	SIR (95% CI)	NO. OF CASES	SIR (95% CI)
0–1	43	1.9 (1.4–2.6)	23	3.6 (2.3–5.5)	66	2.3 (1.8–2.9)
2–4	10	0.3 (0.2–0.6)	6	0.7 (0.3–1.5)	16	0.4 (0.2–0.7)
5–9	26	0.7 (0.5–1.0)	4	0.4 (0.1–1.0)	30	0.6 (0.4–0.9)
10–24	16	0.5 (0.3–0.8)	8	1.1 (0.5–2.1)	24	0.6 (0.4–0.9)
2–24	52	0.5 (0.4–0.7)	18	0.7 (0.4–1.1)	70	0.6 (0.4–0.7)

*CI denotes confidence interval.

1338 underwent surgical treatment for the ulcers during follow-up; their data were thus censored as of the time of operation. Among the patients with both types of ulcer, the standardized incidence ratio for gastric cancer 3 or more years after the index hospitalization was 1.5 (95 percent confidence interval, 0.98 to 2.1), declining from 2.0 (95 percent confidence interval, 0.98 to 3.8) in the period 3 to 4 years after the index hospitalization to 0.8 (95 percent confidence interval, 0.2 to 1.8) in the period 10 to 24 years after hospitalization.

Multivariate Analysis

After we controlled for the influence of other explanatory variables, the standardized incidence ratio for gastric cancer among patients with duodenal ulcers was only one third of that among patients with gastric ulcers (Table 5). The standardized incidence ratios for all patients in the study seemed to diminish with longer follow-up, although this effect, even for patients followed for more than 10 years, was only marginal. Women had a 40 percent higher relative risk of cancer than men, and the youngest patients (those less than 50 years old at the time of the index hospitalization) had a relative risk more than twice that of the oldest (70 years old or more). The relative risk for patients whose index hospitalization occurred in the period 1976 through 1983 was approximately 30 percent lower than that for those hospitalized from 1965 through 1975. Patients who had an endoscopy recorded in the Inpatient Register had a standardized incidence ratio 60 percent higher than those who did not. The Pearson chi-square statistic for the multivariate model was 579.1 with 618 degrees of freedom, which indicates a good fit (the deviance was even smaller). In addition to the main-effects model in Table 5, we also created models to analyze any interactions between ulcer type and other variables. However, no significant interactions were revealed (the variable most likely to alter the effect of ulcer type was the length of follow-up).

DISCUSSION

In this population-based, long-term study of patients with peptic ulcers who had not undergone surgery, we found, among patients hospitalized for gastric ulcers, a risk of gastric cancer almost twice the expected rate; among patients with duodenal ulcers, there was a significant, 40 percent reduction in risk. Patients with prepyloric ulcers had a risk of gastric cancer that was close to the expected value.

The reduced risk of gastric cancer that we found among patients with duodenal ulcers is consistent with clinical observations[18] and with two smaller follow-up studies from Japan.[8,19] The increase in risk among patients with gastric ulcers, on the other hand, has not been seen in most follow-up studies, but these studies were often limited by small samples, short follow-up,[3,4,6,8] or a reliance on radiologic diagnosis,[3,4,6] which is a less precise technique than endoscopy.[20,21]

Any suggestion that there was an unnoted source of bias in our study — whether related to selection, confounding factors, or ascertainment — would have to account for the fact that the presence of ulcers had two opposite effects, increasing the relative risk of gastric cancer among patients with gastric ulcers and decreasing the risk among patients with duodenal ulcers. Moreover, if the positive association of gastric ulcers with gastric cancer was the result of cancers that were misdiagnosed as ulcers, it seems unlikely that the association would persist after more than 10 years of follow-up, particularly since many patients were under close endoscopic surveillance until their diagnosed ulcers healed. It is also unlikely that any screening effect of the work-up for the initial diagnosis would persist after more than 10 years of follow-up and that it would be limited to the cohort of patients with duodenal ulcers. Furthermore, duodenal ulcers frequently recur; patients with the disease are likely to undergo repeated examinations that should facilitate the identification of gastric cancers throughout follow-up and thus counterbalance any delayed effect of initial screen-

TABLE 5. RELATIVE EFFECTS ON THE STANDARDIZED INCIDENCE RATIOS IN THE UNIVARIATE AND MULTIVARIATE ANALYSES, ACCORDING TO SELECTED VARIABLES.*

VARIABLE	UNIVARIATE MODEL	MULTIVARIATE MODEL
	relative risk (95% confidence interval)	
Type of ulcer		
Gastric		
Not prepyloric	1.0	1.0
Prepyloric	0.6 (0.4–0.8)	0.6 (0.4–0.8)
Duodenal	0.3 (0.2–0.4)	0.3 (0.2–0.4)
Length of follow-up		
2–4 Yr	1.0	1.0
5–9 Yr	0.9 (0.7–1.2)	0.9 (0.7–1.2)
10–24 Yr	0.8 (0.6–1.1)	0.7 (0.5–1.0)
Sex		
Male	1.0	1.0
Female	1.6 (1.2–2.0)	1.4 (1.1–1.8)
Complication		
Bleeding	1.0	1.0
Perforation	0.9 (0.6–1.5)	1.0 (0.6–1.6)
None or other	1.1 (0.9–1.4)	1.0 (0.7–1.2)
Age at index hospitalization		
⩾70 Yr	1.0	1.0
50–69 Yr	1.1 (0.9–1.5)	1.4 (1.0–1.8)
<50 Yr	1.7 (1.1–2.7)	2.4 (1.5–3.8)
Year of index hospitalization		
1965–1975	1.0	1.0
1976–1983	0.9 (0.7–1.2)	0.7 (0.6–1.0)
Type of investigation		
No endoscopy	1.0	1.0
Endoscopy	1.5 (1.2–2.0)	1.6 (1.2–2.1)

*These analyses excluded the patients in whom cancer developed in the first two years of follow-up and those with both gastric and duodenal ulcers. The risk for the reference category in each subgroup analysis is defined as 1.0. The standardized incidence ratio for the group of patients with all the reference characteristics — male patients 70 years of age or older who had gastric ulcers (not in the prepyloric region) with bleeding and did not undergo endoscopy, as observed during the third and fourth years of follow-up — was estimated to be 1.7 (95 percent confidence interval, 1.2 to 2.4).

ing. The poor prognosis of gastric cancer also makes ascertainment bias an unlikely explanation.

The data on our cohort include an unknown number of person-years of observation attributable to patients who underwent surgery in the last six years of the study, since we had no information on surgical procedures performed after 1983. However, this uncertainty is unlikely to have affected the estimates of risk because only a small proportion of all patients in Sweden with peptic ulcers had surgery during this period. Moreover, most patients operated on for duodenal ulcers during the 1980s underwent vagotomy, which has been reported as not affecting — or possibly even increasing — the risk of gastric cancer.[22] On the other hand, the patients in our cohort who underwent gastric resection (almost exclusively those with gastric ulcers) were followed for no more than 6 years, and the risk of gastric cancer is decreased during the first 20 years after partial gastrectomy.[23] Thus, any misclassification would lead to underestimating the risk associated with gastric ulcer and overestimating the risk associated with duodenal ulcer.

The cohort was drawn from hospitalized patients, of whom more than 50 percent had complications of ulcers (bleeding or perforation) at the time of their index hospitalization. Many patients with such complications have been found to be users of nonsteroidal antiinflammatory drugs (NSAIDs),[24,25] and there is suggestive epidemiologic evidence that NSAIDs may protect patients against gastric cancer as well as colorectal cancer.[26,27] However, because we found no major differences in the risk of gastric cancer between patients with ulcers who had complications and those who did not, we believe any confounding of our results due to the use of NSAIDs was likely to have been minor. Smoking, another possible confounding factor, has been linked to duodenal ulcers,[28,29] gastric ulcers,[29] and gastric cancer.[30] In our study, we found an increased risk of virtually all types of cancer known to be related to smoking in both the patients with duodenal ulcers and those with gastric ulcers (data not shown), which would indicate that smoking was indeed more prevalent in our cohort than in the general population. Thus, confounding of our results by smoking may well have increased the risk of gastric cancer among the patients with gastric ulcers and counteracted part of the reduction in risk among those with duodenal ulcers.

The malignant degeneration of gastric ulcers appears to be rare.[2,8,31,32] Tumors that are chemically induced in rodents tend to develop in or near ulcers, but the presence of ulcers in rats does not increase the overall incidence of tumors.[33] Thus, although gastric ulcers are probably not a cause of gastric cancer, the positive association between the two diseases suggests they have certain risk factors and precursor states in common.

Duodenal ulcers, on the other hand, seem to be associated with conditions that protect patients against gastric cancer. Close to 100 percent of patients with duodenal ulcers are infected with *H. pylori*,[11] as compared with 40 to 60 percent of the corresponding age groups in the Swedish general population.[34] *H. pylori* — recently designated a carcinogen in humans by the International Agency for Research on Cancer[35] — may affect the early stages of gastric carcinogenesis by inducing chronic gastritis in which there is formation of free radicals by inflammatory cells[36]; production of nitric oxide, nitrates, and nitrosamines by macrophages[37,38]; and increased cell turnover.[39] It seems likely that some factors at work in patients with duodenal ulcers modify the risk of stomach cancer associated with *H. pylori*.

A clue to one such protective factor comes from the observation that whereas multifocal atrophic gastritis predisposes patients both to gastric ulcer disease and to gastric cancer,[40-42] the relation between this type of gastritis and duodenal ulcers is less

clear.[43] *H. pylori* infection is related to atrophic gastritis in groups of unselected patients,[44,45] but the positive association appears more pronounced in patients with gastric ulcers than in patients with duodenal ulcers.[46] Atrophic gastritis, in which there is a loss of gastric acidity, contributes to a gastric bacterial flora that promotes the endogenous formation of *N*-nitroso compounds.[47] Furthermore, the infiltration of leukocytes into the gastric mucosa, combined with an alkaline pH in gastric juice, results in low levels of ascorbic acid[48] and a diminished ability to block the *N*-nitrosation process.[49] Patients with duodenal ulcers, however, are reported to have high levels of ascorbic acid in the gastric juice.[50]

If a risk of gastric cancer is essentially confined to people with gastric atrophy and the risk among them is very high, a seemingly decreased risk will be observed among patients with duodenal ulcers.[51] However, in view of a rate of gastric cancer in patients with pernicious anemia 2.9 times the expected level (in a study[52] with a design similar to our own), it seems unlikely that the excess risk associated with atrophic gastritis is high enough to explain our findings.

It is noteworthy that the increased risk of gastric cancer in patients with gastric ulcers was higher in women than men, and in younger as compared with older patients, even after we controlled for other possible risk factors. In a previous Swedish study of a cohort of surgically treated patients with peptic ulcers, this same pattern of risk of gastric cancer was found.[23] Moreover, in the patients in our cohort with duodenal ulcers, the reduction in the risk of gastric cancer was most pronounced in the two older age groups. However, these data should be interpreted with caution because it is not clear to what extent a patient's age at first hospitalization for ulcers correlates with his or her age at the onset of ulcer disease.

Our findings may have important clinical implications. There is some suggestive evidence that vagotomy, a procedure used mainly for duodenal ulcers, may increase the risk of gastric cancer,[22] as may treatment with cimetidine,[53] with the effect more prominent in women than in men. Our finding of a low base-line risk of gastric cancer among patients with duodenal ulcers sheds new light on these results, since a slight increase in risk reported after surgically or pharmacologically induced hypochlorhydria may, in fact, represent an important excess.

In conclusion, our results suggest that gastric ulcers and gastric cancer have etiologic factors in common. The inverse relation we found between duodenal ulcer disease and gastric cancer further suggests that some processes at work in patients with duodenal ulcers may profoundly modify the carcinogenic effect of *H. pylori* infection.

Supported by a contract (85636-05) with the National Cancer Institute.

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